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CASE REPORT

Deep-brain stimulation of the nucleus accumbens in obsessive compulsive disorder: clinical, surgical and electrophysiological considerations in two consecutive patients

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Abstract Obsessive compulsive disorder is a highly disabling pathological condition which in the most severe and drug-resistant form can severely impair social, cognitive and interpersonal functioning. Deep-brain stimulation has been demonstrated to be an effective and safe interventional procedure in such refractory forms in selected cases. We here report the first Italian experience in the treatment of this pathology by means of nucleus accumbens stimulation, pointing out to some technical data which could be of help in localization of the target.

Keywords Deep brain stimulation · Obsessive–compulsive disorder · Microrecording

Introduction

Electrical stimulation of brain structures was originally introduced in the 1950s as a therapeutic option to treat behaviour disorders or chronic pain conditions [1, 2]. Deep-brain stimulation (DBS), however, only became a widely accepted procedure in the 1990s, when it was introduced for the treatment of advanced and drug-refractory Parkinson's disease [3] and other primary or symptomatic movement disorders. More recently, DBS has been considered a therapeutic option for selected psychiatric disorders. A recent editorial of Goodman and Insel [4] reveals that 50 cases of subjects with obsessive compulsive disorder have been implanted and published since 1999. The DBS option has been selected for OCD patients who have severe chronic treatment-resistant symptoms after several treatment options, i.e. pharmacological (at least 4 different therapies), psychotherapy, and in some cases even ECT, with transient or no results. Many data point to a neurobiological basis for OCD: the evidence for a genetic component in its pathogenesis [5], the frequent detection of acquired or congenital striatal lesions and altered ratio between white and gray matter in this region [5], the differences in brain regional activity detected by neuroimaging between OCD patients and normal subjects [6, 7], the occurrence of the disease in children after streptococcal infection inducing autoimmunity with subsequent basal ganglia damage [8].

A large amount of data point to the role of frontal cortico-subcortical circuit dysfunction in the pathogenesis of the disease [9]. DBS of the nucleus accumbens (NACC) was introduced by Sturm in 2003 to treat patients affected by obsessive compulsive disease (OCD) refractory to conservative treatments such as drugs and cognitive behavioural therapy [10]. The choice of the NACC as a deep-brain target in OCD patients was suggested following advancing knowledge in the field of neurophysiology about human cortico-subcortical circuits, as far as they are compared to experimental findings in animal models, [11] and by anatomo-clinical considerations in patients treated by anterior capsulotomy [12], subcaudate tractotomy [13] and DBS of the anterior limb of the internal capsule [14].

In Italy the first two patients who underwent DBS for OCD were operated on in 2007. This experience was the result of cooperation between Psychiatrists, Neurophysiologists and Neurosurgeons. We report the 2 years (for Patient 1) and 27 months (for Patient 2) follow-up of these patients with regard to selection criteria, surgical methodology, postoperative management and m features.

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Materials and methods

Inclusion criteria were: severe chronic form of treatment-resistant OCD with duration of illness of at least 5 years without remission. Treatments with maximum tolerated dose of at least four out of clomipramine, fluvoxamine, sertraline, paroxetine, fluoxetine for at least 3 months, augmentation strategies with at least two out of lithium, clonazepam, atypical antipsychotics, ECT; psychotherapy simultaneously with pharmacotherapy. A Yale Brown Obsessive Compulsive Scale (Y-BOCS) score of >30/40 and a Global Assessment of Functioning (GAF) Score less than 45 as an index of OCD severity were required to consider the option of surgical therapy.

Subjects who underwent evaluation for DBS were sent to us by their psychiatrists due to the fact that the experimental procedure was communicated to many psychiatric services. DSM IV-TR Diagnostic criteria were used for psychiatric diagnoses. All patients have been treated by several psychiatrists as inpatients and outpatients and their clinical charts were accurately evaluated at the screening visit. Detailed patient screening, record review, interviews with treating clinicians were performed in order to insure that OCD was the primary diagnosis. The presence and severity of OCD symptoms were evaluated by means of Y-BOCS; severity of depressive symptoms was evaluated by means of HAMD21 rating scale. Y-BOCS checklist was used in order to investigate the OCD symptoms. Our clinical protocol did not include a standardized SCID interview for Axis I disorders. A SCID interview was performed for Axis II personality disorders. Exclusion criteria were past or present diagnosis of psychotic disorder, present or past substance abuse, any current clinically significant neurological disorder or medical illness, any clinically significant abnormality on preoperative magnetic resonance imaging, any DBS contraindication. Eligible candidates for DBS were evaluated separately by two psychiatrists and were selected when both agreed on diagnosis and inclusion/exclusion criteria.

Twenty-two patients were evaluated over 3 years; 17 did not satisfy inclusion and/or exclusion criteria for different reasons. Among them three patients who fitted inclusion and exclusion criteria decided to postpone the DBS surgery after the screening visit. Two patients who fitted inclusion and exclusion criteria decided to accept DBS surgery.

Both patients had comorbidities with affective disorders (Patient 1: bipolar disorder, most recent episode depressed; Patient 2: major depressive disorder, recurrent). Both of them were male.

Patient 1 is a 33-year-old unemployed man who has suffered from OCD since the age of 16. When he was 30 a diagnosis of bipolar disorder type I was added in Axis I. In 2003 he underwent ECT because of severe depressive symptoms. The patient had several psychiatrists and each of them changed therapies, frequently with add-on strategies. The only period of relief of symptoms since the beginning of the illness was after the introduction of lithium in his pharmacotherapy, though this lasted only 5 months. At the time of the first evaluation he suffered from mental obsessions in the form of a recurrent mental image of a house that caused him anxiety from which he compulsively imagined escaping, checking external reference points. The total preoperative score on the Y-BOCS was 38. The GAF score was 40. Depressive symptoms were rated with the Hamilton Rating Scale for Depression (HAM-D) and the score was 25. At the first evaluation, before study entry, he was treated with lithium 1,000 mg, gabapentin 900 mg, quetiapine 300 mg, aripiprazole 5 mg, levomepromazine 12.5 mg.

Patient 2 is a 41-year-old unemployed man who has suffered from OCD since age 15. Comorbidities with body dysmorphic disorder, phobic anxiety disorder, major depressive disorder were diagnosed. Five years before the intervention he underwent ECT. At the time of enrolment he suffered from dubitative obsessions regarding his body (the dimension of his head and of his wrists), his personal history and his psychiatric diagnosis, auto- and hetero-aggressive obsessions, compulsive checking of various parts of his body. His mood was low, he abused alcohol. The total score on the Y-BOCS was 30/40. The GAF score was 41. At study entry he was only treated with clordemetildiazepam (1 mg). HAM-D score was 27. This patient lost all hope in therapies and decided to stop all medication.

Surgery and targeting procedure

After a detailed explanation of procedure and explanation of potential adverse events, the two patients signed written consent to surgical intervention.

T1, T2 and IR MRI brain images were obtained preoperatively for the two patients; the morning of surgery, under general anaesthesia, a Leksell G frame was applied and a CT scan performed. After adequate merging of the two exams in a neuronavigation system (Medtronic, Minneapolis, USA) and use of direct and indirect targeting techniques (performed on a separate computer), the two methods were compared with respect to the coordinates of the nucleus accumbens, and the final target coordinates for both patients resulted to be: ± 3 mm lateral to ICP, $+16$ mm anterior to MCP and 2 mm inferior to ICP. Two coronal burr holes were made on each side 3.5 cm lateral to midline.

A rigid cannula was inserted through the cranial burr holes on each side and positioned up to 10 mm from the

target; continuous physiological recordings then began, being performed by means of a Medtronic Leadpoint TM system (Medtronic Inc., Minneapolis, MN, USA). An exploratory trajectory was made by extruding the microelectrode using 0.5 mm steps. At the end of the exploration the rigid cannula was used as a guide for placement of the definitive electrode (DBS-3389; Medtronic Inc., Minneapolis, MN, USA).

No side effect was noted during the insertion procedure and there was no perioperative adverse event for either of the two patients. During the same surgical session, two pulse generators (Soletra, Medtronic) were implanted in the subcutaneous tissue of subclavian region on each side for both patients.

Microrecording

Data analysis

Neurons with stable activity recorded for at least 10 s were analysed. Postoperative data analysis was performed by the Spike2 analysis package (CED, Cambridge, UK). Single-unit events were discriminated, and confirmed to arise from a single neuron using template-matching spike sorting software. The results were inspected for the accuracy of spike identification, with inappropriate identified spikes reclassified individually or the spike sorting repeated. The mean firing rate was calculated by dividing the total number of the isolated spikes by the length of the recording. Correlation histograms had a bin width of 5 ms and lags up to 1,000 ms. The recurrence of peaks and troughs at regular interval was the expression of the oscillatory activity of the spike train. The oscillation's frequency was determined by calculating the reciprocal of the peak-to-peak time interval of two consecutive peaks. Random discharge was identified when the autocorrelogram exhibited no regularity in the occurrence of peaks and troughs.

Spontaneous activity from 48 cells was recorded along four trajectories (2 in each patients, 1 in each side). However, 34 units had a good signal-to-noise ratio and were further analysed. Fourteen cells (41%) showed firing rates higher than 10 Hz, while the remaining had firing rates lower than 10 Hz.

At the beginning of each trajectory no action potentials were recorded for 3–5 mm, indeed low-frequency discharge (about 5 Hz) cells were encountered, intermingled with a few units discharging at higher rates (about 15 Hz). At the end of each trajectory there was an increase in background noise and all the recorded units fired at very high rates. These neurons fired at a very high rate (30 Hz ca), and were easily distinguished from NA activity (Fig. 4). In our opinion, these activities could be attributable to the anterior limb of internal capsule, NA and subgenual cortex, respectively (Fig 4). With the exception of two units displaying some kind of regularity in the discharge pattern, the remaining units fired in a random fashion. Postoperative trajectory reconstruction showed that these units were recorded between 2 and 3 mm above the subgenual cortex.

Stimulation parameters and active contacts

Taking into account the definitive position of the electrodes and the anatomical considerations (see "Discussion" section), the final parameters chosen for long-term stimulation were: 5 V, 90 μs 130 Hz, case positive and central contacts (1 and 2) negative for Patient 1, and 5.5 V, 90 μs, 130 Hz, case positive and central contacts (1 and 2) negative for Patient 2.

Results

In the postoperative period, a volumetric brain CT scan was obtained for the two patients and merged with preoperative brain MR scan; in both cases the correct positioning of the intracerebral electrodes was confirmed (Figs. 1, 2).

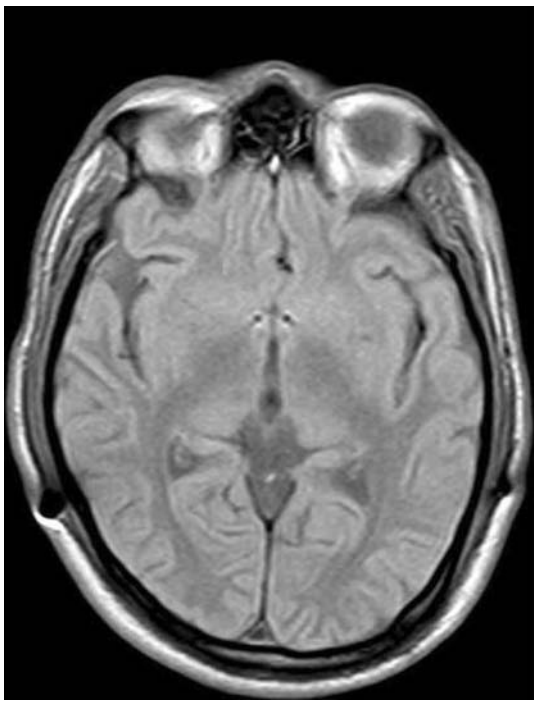

Fig. 1 Postoperative brain MRI axial slice showing the definitive position of nucleus accumbens electrodes in Patient 1

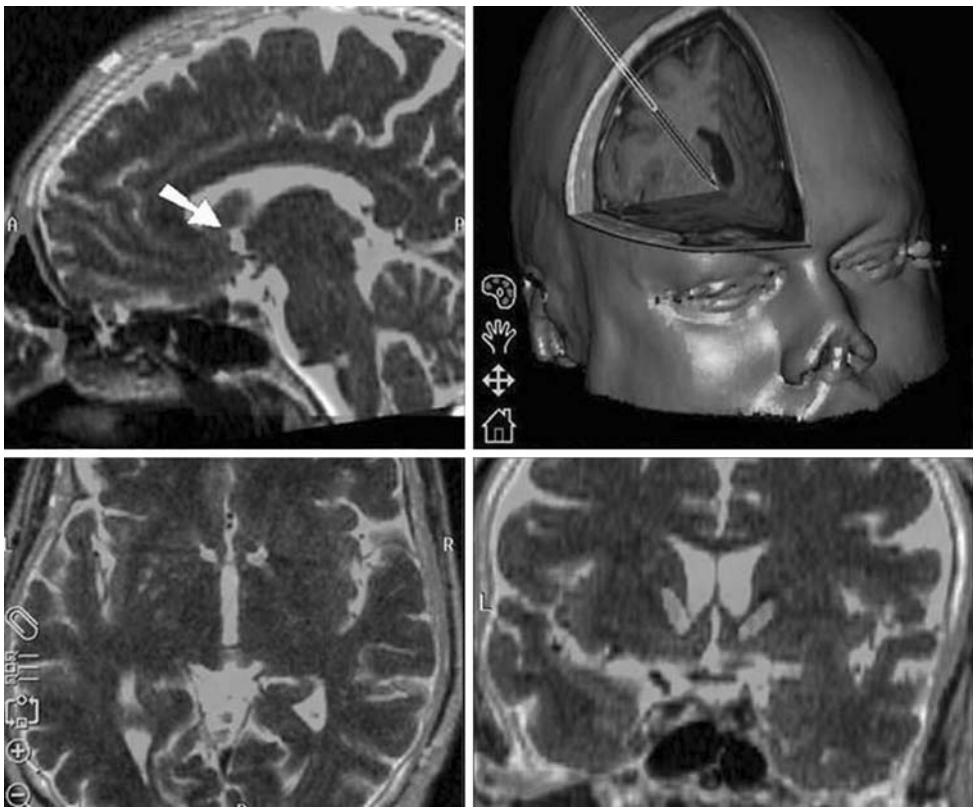

Fig. 2 Postoperative images of Patient 1, obtained through merging preoperative MRI with postoperative CT and showing the correct positioning of nucleus accumbens electrodes bilaterally in sagittal, coronal and axial scans

Clinical outcome at 2-year follow-up for Patient 1 and at 27 months for Patient 2 is represented in Fig. 3 and Table 1. Both patients presented a slow but evident clinical improvement of both obsessive–compulsive and depressive symptoms and general functioning. In Patient 1 the major part of improvement was reached after the first year of stimulation and then remained stable in time, while Patient 2 showed a significant improvement only after 22 months, when the parameters of stimulation were modified (see section below).

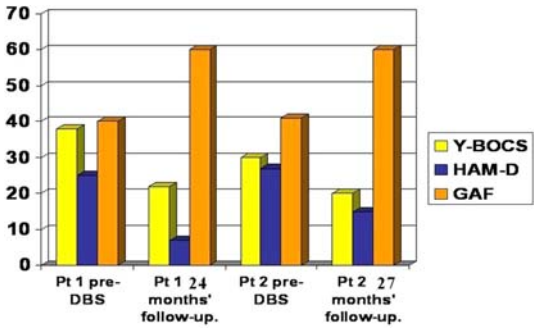

Fig. 3 Clinical outcome with respect to preoperative period for each of the two patients. At each time point, the first row indicates Y-BOCS score, the second row HAM-D score, and the third row indicates the GAF score

Discussion and conclusions

DBS has been introduced to treat patients who have a severe chronic treatment-resistant OCD causing family and social life impairment. In the past, as far as neurosurgery is concerned, only ablative procedures such as capsulotomy [12] and cingulotomy [15] were considered therapeutic options in some countries (but not in Italy). On the other hand, DBS of the ventral striatal region introduced in the North European countries was also quite widely practised in the USA [16]. The reversibility of the procedure made this approach ethically acceptable in our country too, where any kind of surgical procedure for behaviour and psychiatric disorders has not been employed since the end of the 1960s.

Table 1 Numeric data of the Y-BOCS, HAM-D and GAF scores of the two patients at preoperative period and at last follow-up clinical examination

	Patient 1		Patient 2	
	Pre-DBS	24-months follow-up	Pre-DBS	27-months follow-up
Y-BOCS	38	22	30	20
HAM-D	25	7	27	15
GAF	40	60	40	60

The role of the nucleus accumbens in OCD has been hypothesized on the basis of experimental studies and on the basis of the improvements obtained by DBS in several series of patients reported in literature [9]. Our experience confirms these data, focusing attention on the core of the nucleus accumbens which constitutes the most cranial portion of the nucleus itself, lying very close to the fibers of the anterior limb of the internal capsule and below the caudate nucleus (Fig. 4). The chronic stimulation of the shell component of the accumbens which lies inferior to the core was less effective than the stimulation of the core. This observation was made taking into account anatomical considerations, the postoperative images of the patients and the active contacts employed. In fact Patient 2, who had not improved after 2-year stimulation of the accumbens shell, experienced a significant clinical recovery after battery replacement when the stimulation contacts were changed and the accumbens core was targeted. In this report we suggest an intraoperative neurophysiological methodology which allows the localization of the core of nucleus accumbens along the stereotactic trajectory: it is localized at about 7 mm cranial to the subgenual cortex, which can be recognized by microrecording along the stereotactic trajectory (Fig. 4). Another observation can be made about the choice of the electrical parameters delivered at the definitive target: in both cases the therapeutic effect started when the current amplitude was set over 5 V, keeping the remaining parameters constant (130 Hz, 90 μs PW). This finding may suggest the need for a large electric field (estimated to be between 4 and 5 mm of diameter from the axis of the active contact in unipolar stimulation), considerably wider than the one which is obtained in subthalamic nucleus stimulation for advanced Parkinson disease (1.5–3 V, 130 Hz, 90 μs PW). Hence, the therapeutic effect may also depend on the stimulation of anatomic structures surrounding the nucleus. The need for high-frequency stimulation (>100 Hz) to obtain therapeutic effects does not seem different from what happens in other DBS applications such as PD, tremor, dystonia and cluster headache, where low-frequency stimulation (<80 Hz) has proven to be ineffective. It has been hypothesized that HFS mimics a lesion resulting in a reversible interruption of a circuit or in a reversible inhibition of discrete neuronal pools (although several other hypotheses have been made about this) [17]. This action is, however, in line with the evidence of a hyperfunctioning of the orbitofrontal cortex–ventral striatum–ventral pallidum–medial thalamus–orbitofrontal cortex subcircuit of the basal ganglia system. In fact, this subcircuit seems to act as an internal generator of the feeling of unease in strict relation to reward detection and motivational and emotional aspects of decision making, working together with the anterior cingulate cortex and its connection loops. Striatosomes, discrete neuronal pools present in the ventral striatum, are mainly involved in the above-mentioned circuit through the direct pathway, whereas matrisomes interact with premotor and associative cortico-subcortical loops through the indirect pathway [18]. An inappropriate hyperfunctioning of the first loop, due to several causes (including a hyperactivation of the direct pathway with respect to the indirect pathway, or a lesion at crucial structures in the system leading to diminished inhibition of orbitofrontal loop or diminished activity of associative loop) could contribute to the internal sensation that "something is wrong", then leading to the clinical

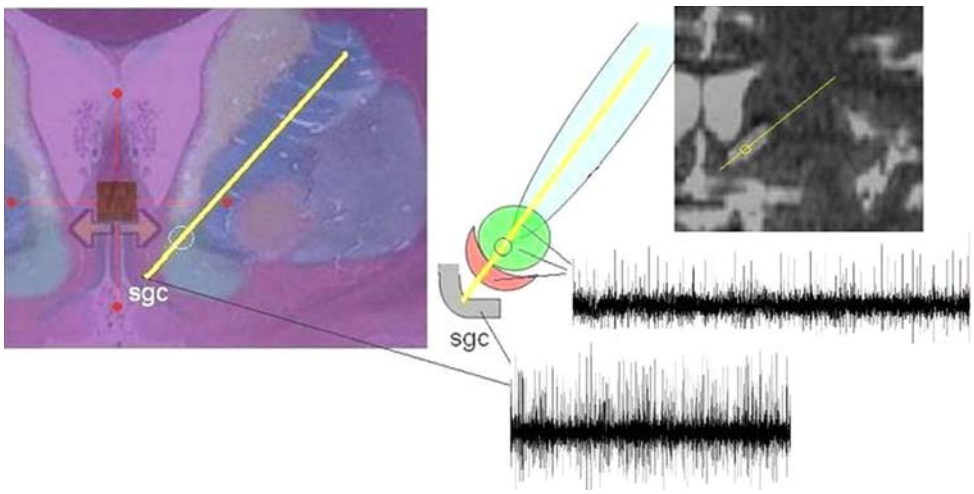

Fig. 4 *Left* Schematic drawing in the Franzini Atlas of the trajectory used for the targeting of nucleus accumbens; note the position of the subgenual cortex (*sgc*) with respect to nucleus accumbens (immediately above *sgc*). *Center* Trajectory encompassing nucleus accumbens' core (*circle*) and shell (*half-moon*) and finally *sgc*: note the difference in discharge rate, which is clearly higher in *sgc* if compared to nucleus accumbens. *Right* Postoperative CT merged with preoperative MR in coronal view showing the trajectory of the electrode at this site

manifestations of OCD [9]. An alternative explanation addresses the role of the nucleus accumbens in action selection circuits. In particular, it has been suggested [19] that the dopamine in the NA facilitates the ability to respond to unpredictable stimuli, which requires interruption of the ongoing behaviour. In fact according to this model the basal ganglia action selection circuits are hierarchically divided: basal ganglia circuits that process limbic information (involving NA and the dorsomedial striatum), which decide the general course of action, and other circuits involving more dorsal and dorsolateral striatal areas, which decide specific actions to take according to the goal and general action plan set by the limbic circuits. When a new, unpredictable stimulus is perceived, the highest (limbic) level of the basal ganglia hierarchy sets action priorities for the decisions made by the lower levels when stimuli once again become predictable.

Capturing the salience of an unpredictable stimulus is the key to developing new actions. According to Redgrave et al. [20] dopamine signals may have the role of identifying which aspects of context and behavioural output are crucial in causing unpredicted events. The repetition of the set of actions which immediately preceded the unpredicted event leads to the development of entirely novel and adaptive responses. We can hypothesize that in OCD patients, predictable stimuli are perceived as unpredictable stimuli by a hyperfunctioning NA. This aberrant signalling causes the highjacking of the ongoing behaviour by a fixed pattern of thoughts/actions stored in more dorsal striatum. Restoring the correct phasic dopaminergic signalling by DBS in NA could thus prevent the intrusion of obsessions and compulsions in the patient's mind.

It has to be remarked that OCD symptoms may also improve with chronic stimulation of other anatomic structure within the limbic system such as the ventral portion of the Stn [21], and the anterior limb of the internal capsule [14]. It is worth noticing that in Mallet et al's. manuscript [21] the authors reported the occurrence of 15 serious adverse events in their case series, with one intracerebral haemorrhage and two infections.

We hypothesize that the accumbens core nucleus is a node of the above-mentioned network within the limbic system and that this network may be modulated by electrical stimulation or interrupted by ablative procedures in several anatomic sites including mainly the cingulum, the internal capsula, the medial thalamus, the subthalamic nucleus and the accumbens core nucleus.

DBS of the accumbens core nucleus seems a promising treatment for refractory OCD, and its reversibility has made this technique ethically acceptable in severely impaired patients refractory to any kind of conservative treatment. However, additional long-term controlled studies are needed to demonstrate DBS efficacy in treatment of resistant OCD. Moreover, the need of a considerable amount of electrical current delivered continuously raises the problem of battery replacement which may need to take place every 2–3 years and although this requires only a minor surgical procedure performed under local anaesthesia, it may represent a limitation of this treatment, particularly when the exhausted battery induces relapse of symptoms and anxiety. Newly introduced rechargeable devices may partially resolve this problem, requiring only weekly transdermal chargeable procedures.

Further investigations are also required to better understand the mechanisms of clinical response to DBS, and to address other issues, such as the role of intraoperative neurophysiology in the prediction of long-lasting clinical effects, and the identification of clinical variables predicting good outcome. Finally, we would like to stress the need for a multidisciplinary team involved in the management of these patients and the specific role of psychiatrists in both the selection procedure and in the follow-up evaluation.

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